The use of tocilizumab and tofacitinib in patients with resolved hepatitis B infection: a case series

The use of immunosuppressive medications in people with hepatitis B virus (HBV) infection is associated with an increased risk of HBV reactivation, which can lead to liver failure and death. Tumour necrosis factor inhibitors, rituximab and other biologic treatments have been associated with HBV reactivation in up to 24% of people with resolved HBV (positive core antibody (HBcAb), negative surface antigen (HBsAg) and positive or negative surface antibody (HBsAb)) and 34% of people with chronic HBV (positive HBsAg); reactivation risk varies based on HBsAb status.[1–3] Both tocilizumab (interleukin-6 (IL-6) receptor inhibitor) and tofacitinib (Janus kinase (JAK) inhibitor) interfere with IL-6 signalling, which moderates immune control of chronic HBV. Although HBV reactivation has been reported with tocilizumab and tofacitinib in Asia, limited data describe this risk in the USA.[4]

We performed a retrospective study of people who were prescribed tocilizumab or tofacitinib and had resolved or chronic HBV infection between 1995 and 2018 in the Partners Health Care System (PHS).[5] We extracted relevant variables from the electronic health record and defined HBV reactivation as: a greater than 10-fold increase or an absolute increase greater than 10^5 copies/mL in HBV DNA level from baseline or a positive HBsAg when previously negative. This study was considered exempt by the PHS Institutional Review Board.

Of the 20 people identified, all were HBcAb positive and HBsAg negative. Four received tofacitinib and tocilizumab sequentially such that there were 24 medication exposures. Sixteen patients (67%) received tocilizumab and eight patients (33%) received tofacitinib (table 1). Everyone treated with tocilizumab (16, 100%) and seven (88%) of those prescribed tofacitinib were HBsAb positive. The median age at treatment initiation was 59.4 years (tofacitinib) and 66.1 years (tocilizumab), and the majority were female in both groups. In each group, the most common diagnosis was rheumatoid arthritis, 75% received concurrent rheumatic disease medications and 25% received entecavir or tenofovir within 2 years of tocilizumab or tofacitinib (table 1).

Median follow-up time after treatment initiation was 4.0 years (IQR: 1.6–5.9) (tocilizumab) and 3.1 years (IQR: 0.9–5.7) (tofacitinib). During follow-up, all had aminotransferases measured at least once; in 63% (tocilizumab) and 38% (tofacitinib), aminotransferases were checked at least four times annually for 2 years. Six experienced mild, transient aminotransferase elevations and one had severe elevation (>10× normal) attributed to ischaemic injury; none were attributed to HBV reactivation. Among those with HBV DNA or HBsAg assessed after treatment initiation (88% in the tocilizumab group, median 3 tests; 75% in the tofacitinib group, median 2.5 tests), none were positive.

In conclusion, we observed no episodes of HBV reactivation in people with resolved HBV infection treated with tocilizumab or tofacitinib with over 3 years of follow-up time in a US healthcare system. The majority were HBsAb positive, which reduces but does not eliminate reactivation risk; HBV reactivation occurs in up to 6% of people with HBsAb/HBcAb positivity receiving

Table 1 Demographics, clinical characteristics and follow-up of study population

Characteristic	Tocilizumab-treated patients (N=16)	Tofacitinib-treated patients (N=8)
Age (years); median (IQR)	66.1 (45.4–71.3)	59.4 (42.4–70.9)
Female, n (%)	9 (56)	7 (88)
Race, n (%)		
White	7 (44)	3 (38)
Black or African–American	4 (25)	4 (50)
Asian	4 (25)	0 (0)
Unknown/other	1 (6)	1 (12)
Ethnicity, n (%)		
Non-Hispanic	15 (94)	8 (100)
Unknown	1 (6)	0 (0)
Diagnosis for medication indication, n (%)*		
Rheumatoid arthritis	10 (63)	7 (88)
Psoriatic arthritis	0 (0)	1 (13)
Giant cell arteritis	3 (19)	0 (0)
Lymphoma	2 (13)	0 (0)
Adult-onset Still's disease	1 (6)	0 (0)
Disease duration (years), median (IQR)	3.6 (1.1–10.5)	7.6 (2.9–17.5)
Baseline positive HBV serologies, n (%)		
HBcAb	16 (100)	8 (100)
HBsAg	0 (0)	0 (0)
HBsAb	16 (100)	7 (88)
Baseline HBV DNA assessed	10 (63)	6 (75)
Comorbidities†	1 (6)	1 (13)
Cirrhosis, n (%)	5 (31)	1 (13)
Diabetes	7 (44)	4 (50)
Hypertension	2 (13)	1 (13)
Coronary artery disease		
Time receiving medication (years), median (IQR)‡	1.4 (0.2–4.2)	0.8 (0.4–1.2)
Follow-up time (years), median (IQR)§	4.0 (1.6–5.9)	3.1 (0.9–5.7)
Concurrent immunomodulatory therapy, n (%)¶	12 (75)	6 (75)
Oral glucocorticoids	7/12 (58)	4/6 (67)
csDMARD	7/12(58)	4/6 (67)
Rituximab	1/12 (8)	0/6 (0)
Antiviral treatment,n (%)**	4 (25)	2 (25)
Reactivation of HBV during follow-up, n (%)*		
Yes	0 (0)	0 (0)
No	14 (88)	6 (75)
Unknown (no follow-up HBV DNA or HBsAg)	2 (13)	2 (25)
Number of repeat HBsAg and/or HBV DNA tests, median (IQR)	3 (1–6)	2.5 (0.5–7)

*Percentages do not add up to 100% due to rounding.
†Comorbidities were defined by presence of the diagnosis in the electronic health record.
‡Time receiving medication refers to the time from medication initiation to the discontinuation time as determined by electronic health record notes or the time of manuscript submission for patients still receiving the medication.
§Follow-up time refers to the time from the initial medication prescription to the most recent patient encounter in our healthcare system.
¶Percentages do not add up to 100% as some patients received multiple types of immunomodulatory medications within the 2 years following medication. csDMARDs included methotrexate, leflunomide and sulfasalazine in the tocilizumab group and methotrexate and sulfasalazine in the tofacitinib group.
**Refers to patients who received antiviral treatment at any point within the 2 years following medication. In the tocilizumab group, three patients received entecavir and one received tenofovir, one of which was after the study medication. In the tofacitinib group, one patient received tenofovir and one patient received entecavir, though both after study medication.
csDMARD, conventional syntheticdisease-modifying antirheumatic drug; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.;

rituximab.[1] Pretreatment HBV screening remains important because of the theoretical risk of reactivation.[1–3 6] A quarter of people in our study were prescribed antivirals, reflecting the uncertainty regarding best practices for patients with resolved HBV. Limitations of our study include no cases of chronic HBV, lack of HBV genotype data, small sample size, lack of a control group and use of antiviral therapy by 25%. Our findings suggest that tocilizumab or tofacitinib may be safely used in patients with resolved HBV infection, particularly in those who are HBsAb positive.

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